

## Recommendations for Randomised Trials in Surgical Oncology

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# Recommendations for randomised trials in surgical oncology

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## **Abstract**

### **Introduction**

Trials of surgical procedures in the treatment of malignant disease face a unique set of challenges. This review aimed to describe recommendations for the design, delivery and reporting of randomised trials in surgical oncology.

### **Methods**

A literature search was performed without date limits to identify articles related to trial methodology research in surgery, and surgical oncology. A narrative review was framed around two, open National Institute of Health Research portfolio trials in colon and rectal cancer: the STAR-TREC trial (ISRCTN14240288) and ROCCS trial (ISRCTN46330337).

### **Results**

Twelve specific challenges were highlighted: Standardisation of technique; Pilot and feasibility studies; Balancing treatments; The recruitment pathway; Outcome measures; Patient and public representation; Trainee-led networks; Randomisation; Novel techniques and training; Learning curves; Blinding; Follow-up. Evidence based recommendations were made for future design and conduct of surgical oncology trials

### **Conclusion**

Better understanding of the challenges facing trials in the surgical treatment of cancer will accelerate high quality evaluation, and rapid adoption of innovation for the benefit of patient care.

## Highlights

- Trials in surgical oncology face a unique set of challenges in their design, conduct and delivery.
- Methodological research and experiential learning have increased the volume and quality of pragmatic surgical trials over the past two decades.
- This narrative review frames recommendations for trials in surgical oncology around two NIHR portfolio trials (STAR-TREC and ROCSS)
- Better understanding these challenges will accelerate evaluation of complex surgical interventions.

## **Introduction**

Trials in surgical oncology are characterised by the evaluation of surgical, or interventional procedures in at least one treatment group. They include patients undergoing curative or palliative treatment for malignant disease. The complexity of trials involving surgical interventions has historically led to a paucity of randomised evidence in the surgical management of cancer (1, 2). Unique challenges arise in each phase of the research pathway; from protocol design, to the recruitment consultation, randomisation, blinding, standardisation of the experimental intervention, outcome selection and assessment, ethics and reporting. This has led to failure to recruit patients into surgical trials (3), introduction of bias (4), discontinuation of trials (5), and misreporting (6-8).

Twenty years ago, a systematic review demonstrated that the proportion of treatments supported by randomised evidence in surgery was almost half that of general medicine (9). Efforts to better understand this complexity have improved the quality and volume of surgical trials since this time. Specific recommendations have been made to improve the way surgical trials are designed, delivered and reported (10), but a number of practical difficulties persist. This article describes contemporary recommendations in the design, conduct and reporting of randomised trials in surgical oncology.

## Methods

A narrative review was synthesised, describing challenges and recommendations for design, delivery and reporting of randomised trials in surgical oncology. A literature search was performed using PubMed and OVID via Medline, with the MeSH terms “surgical” OR “surgery” OR “surg\*”; AND “trial” OR “randomised”; AND “methodology” OR “design” OR “conduct” OR “recruitment” OR “reporting” (last accessed: 1<sup>st</sup> June 2017). No date restrictions were imposed. Non-English language papers were excluded. The ‘related articles’ function, references and citation lists were used to identify additional relevant content.

The review framed around two examples of surgical trials in colon and rectal cancer from the National Institute of Health Research portfolio (11):

1. STAR-TREC: Can we save the rectum by watchful waiting or transanal surgery following (chemo)radiotherapy versus total mesorectal excision for early rectal cancer? (ISRCTN14240288)
2. ROCSS: Reinforcement of Closure of Stoma Site. A randomised controlled trial of reinforcement of closure of stoma site using a biological mesh (ISRCTN46330337).

Themes were illustrated with practical examples from the two trials.

## **Trial example 1: STAR-TREC**

*Can we save the rectum by watchful waiting or transanal surgery following (chemo)radiotherapy versus total mesorectal excision for early rectal cancer? (ISRCTN14240288)*

### **Trial summary**

STAR-TREC (12) is a multicentre international randomised, 3 arm-parallel, phase II feasibility study in patients with biopsy proven adenocarcinoma of the rectum (IDEAL phase 2B(13)). Patients with rectal cancer, staged by CT and MRI as  $\leq$  cT3b (up to 5mm of extramural spread) N0M0 can be included. STAR-TREC will assess the ability to recruit to a large, IDEAL phase 3, multi-centre randomised trial comparing radical surgery versus organ saving treatment (Figure 1). Participants are randomised in a 1:1:1 ratio to receive:

1. Conventional total mesorectal excision (TME) surgery (control).
2. Organ saving treatment using long course concurrent chemoradiation (CRT).
3. Organ saving treatment with short course radiotherapy (SCRT).

Following initial organ saving treatment (groups 2 and 3), clinical response to (chemo)radiotherapy determines the next treatment step. Complete clinical response leads to a strategy of watch and wait. A good but incomplete response is followed by transanal microsurgery to remove the portion of the bowel wall affected by tumour. Little or no response is followed by TME. The primary outcome in phase II is the ability increase international recruitment to level that would sustain a larger phase III study incorporating pelvic failure as the primary endpoint. This corresponds to four

cases per month in year 1, rising to 6 per month by the end of year 2. A summary of challenges and recommendations can be found in Table 1.

## **1. Standardisation of technique**

The Medical Research Council guidance for developing and evaluating complex interventions recommends that investigators 'consistently provide as close to the same intervention as possible' by 'standardising the content and delivery of the intervention' (14). STAR-TREC compares stable interventions with which surgeons will already have reached a standard of expertise (TME or TEMS). However significant technical variation can still exist in the provision of these interventions, even within a single hospital. Trial design must strike a balance between a pragmatic design; a real-world comparative effectiveness study (15), allowing technical and non-technical variation in the way in which a surgical intervention and periprocedural care is delivered, and an explanatory approach; a design which requires a homogenous population, strict standardisation of interventions, and comparison of efficacy to a placebo or sham group. Variation can occur not only in the tested surgical procedure but also in the timing and delivery of concomitant interventions, for example general and regional anaesthesia, chemoradiotherapy, and the provision of intensive care support. A complex surgical intervention with multiple components can act inter-dependently or independently to influence outcomes (16). In a pragmatic randomised trial the fidelity of an intervention must be sufficient to ensure the experimental intervention is being uniformly tested, but not so prescriptive that translation into real-world practice is not possible. Tools such as PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2) have been used to model the 'pragmatism' of a trial across phases of its design, and judge the extent to which effectiveness, rather than efficacy is being tested (17).



Description of the technique is also important to ensure robust meta-analysis (16). 30% of surgical trials only report the name of the procedure, without further detail of the procedural steps, or standardisation (18). There are three ways to describe a surgical intervention: 1. By the overall technical purpose of an operation (e.g. removal of the appendix); 2. By its key component parts; 3. By the steps within each component part (19). Direct observation, video-monitoring, or semi-structured interviews with surgeons performing a procedure can help to define these (20). For each step or component, it must be decided which are mandatory, prohibited, or optional and the degree of flexibility allowed within this structure. These must be described fully in the study protocol including the context of intervention delivery and operator expertise according to CONSORT-NPT guidelines (18, 21). Recording of essential and prohibited steps is essential to ensure that patient-level meta-analysis can be conducted, and interventions can be readily adopted into practice (22, 23). In a 2013 review (22), only 34% of non-pharmacological trial interventions had further information available online, and much was inaccessible. Monitoring of adherence to these will allow assessment of the fidelity of the surgical intervention, and identify protocol violation (16). This can be performed using video, or photographic evidence, direct observation or self-reporting.

STAR-TREC has specific Quality Assurance measures embedded into the study protocol that will allow monitoring of the delivery a standardised technique for TME, TEMS and chemoradiotherapy. These include a pre-trial facility questionnaire, process document, and benchmarking cases, and within-trial standardised histopathological assessment, individual case review and intraoperative case record forms.

***Recommendation:*** *A pragmatic design in surgical trials facilitates the direct implementation of effectiveness data into practice. Standardisation of a procedural technique with a structured typology ensures high-quality reporting and patient-level meta-analysis.*

## **2. Pilot and feasibility studies**

Feasibility studies are used to test the deliverability of a full, randomised controlled trial. This includes the clinician and patient acceptability of interventions, the ability of research staff to randomise, outcome selection and assessment, minimal clinically important differences, and the robustness of pathways for follow-up. Pilot studies are miniature versions of a main trial. As such they typically involve a small cohort of patients (commonly around forty (24)), use outcome measures which facilitate the delivery of the main trial, but importantly are not powered to test the research hypothesis. Internal pilot studies run seamlessly into a main trial, but don't allow for large-scale adaptation of the trial protocol following interim analysis. External pilot studies pause for analysis before running into an externally funded phase III trial, so facilitate more radical changes to a study protocol (e.g. change of the primary outcome measure). Pilot studies may facilitate sample size and power calculations for a phase III trial (25), in conjunction with reported event rates from the literature. In trials in surgical oncology where complex interventions are tested, feasibility and pilot studies allow an assessment of the deliverability of a trial, ahead of a full phase III study.

In STAR-TREC the co-primary outcome measures for the phase III trial will be pelvic cancer recurrence, and change in a selected disease-specific quality of life measure (e.g. EORTC QLQ CR29 & C30). However, for the feasibility study (which includes

an external pilot phase), the primary outcome measure is the number of patients recruited to the study. This was selected due to unanswered questions regarding the delivery and design of the main trial, for example:

- would patients understand the trial interventions?
- would clinicians be able to adequately describe equipoise?
- would intensive follow-up be possible following the organ-sparing treatment?

Funding bodies are increasingly recognising the importance of feasibility and pilot studies in reducing research waste, with specific funding sources readily available.

***Recommendation:*** Consider a feasibility study, with an internal or external pilot phase, where there is uncertainty about the deliverability of a main trial.

### **3. Balancing treatments**

Explaining the comparison of two very different treatments to patients can be challenging. Surgeons may inherently favour operative management, as they are invested in their technique and training, and are more familiar with consenting a patient for operative treatment (26). As such, surgeons can struggle to present a non-operative strategy in a balanced light, even where community equipoise is present (27). The successful recipe for presenting balanced treatments requires clinician and/or community equipoise, and a pre-prepared description of interventions being tested, supplemented by a well-designed 'Patient Information Sheet' (PIS)(28).

Patients often have treatment preferences, and this can impact on the ability to recruit and lead to reporting or detection bias(29). Patient preconceptions regarding a treatment, or preference towards one arm can be gently tested during the informed

consent process. It is the clinician's duty to ensure that the patient does not have *incomplete knowledge* upon which they are based their preference. Restoring equipoise can be assisted by exploring false beliefs about one, or both study groups, and providing details and figures to restore balance. When balancing treatments, it is important to discuss differences in future outcome assessment and follow-up as well as the interventions themselves, and the potential impact of this. For instance, in STAR-TREC those undergoing organ-sparing therapy required more intensive follow up than those undergoing primary TME (clinical examination with flexible endoscopy and magnetic resonance imaging every 3 months), which may potentially be disruptive to their working and family lives. Leaving time for patients to think about the implications of being in a trial is mandated in most trials of elective interventions. In trials of emergency care (e.g. emergency laparotomy for a perforated colonic cancer), window periods can be shortened or consented deferred until after surgery, conditional upon impaired capacity at the time of presentation, and pre-approval by local and national ethics committees.

***Recommendation:*** *Prepare balanced explanations for both operative and non-operative treatments. Restoring patient equipoise is possible if they have incomplete information about one of both of the study arms.*

#### **4. The recruitment pathway**

Patients want to be offered the opportunity to be involved in high-quality research. In a UK survey of two large cancer centres, 91% of respondents thought patients should be involved in research, and half agreed to be randomised to a comparative effectiveness study (30). Clear communication and an informed consent pathway

adherent to standard Good Clinical Practice consent guidelines has been demonstrated to increase recruitment rates to trials in cancer therapy (31, 32).

The recruitment consultation is a core component of the recruitment pathway. Core components include: 1. Normalising the research process, 2. Describing clinical equipoise, 3. Balancing treatments, 4. Exploring preferences, 5. Communicating the purpose and process of randomisation. Terminology regarding allocation and randomisation can be particularly troubling for patients, who may feel they are 'losing out', that you are not taking their condition seriously ('flip of a coin', or 'roll of a dice'). Conversely patients may believe that a computer is assigning them a treatment based on any one of their or their disease characteristics. Involving patients as partners in research has been demonstrated to create a more positive recruitment consultation experience(33). Doctors and nurses may also display unease in approaching patients for research consent, especially if unfamiliar with eligibility criteria, unsure about effectiveness of interventions, or if conflict exists between their research and clinical commitments (34).

It is important to recognise that the recruitment consultation is just one part of the informed consent process. In STAR-TREC eligible patients receive a patient information sheet at the earliest opportunity. Eligible patients are identified as part of multidisciplinary team meetings by the study team, with leadership from cancer surgeons in specialist and non-specialist centres playing a crucial role (35-37). The recruitment pathway generally incorporated several interviews based around outpatients and the endoscopy suite, allowing time for the exchange of information.

Once a study has opened it is important to monitor screening logs of eligible patients and recruitment rates across all centres. Where recruitment in surgical trials is failing

specific qualitative interventions have been described (33, 38, 39). The most commonly reported causes of recruitment failure included unease with randomisation, a perceived loss of autonomy, poor understanding of the research, and mistrust of the recruiting clinician (40). STAR-TREC has prospectively considered monitoring of randomisation, with visits to be triggered by lower than expected recruitment from screening logs, poor data quality, or excessive number of participant withdrawals or deviations.

Targeting good recruitment practices can begin early. Evidence-based training courses such as Generating Student Recruiters for Randomised Trials (41) train delegates (medical students and postgraduate trainees) how to communicate equipoise and randomisation as part of an informed consent process.

***Recommendation:*** *Embed recruitment training into your site set-up package. Once set-up, identify sites where recruitment rates are low, and provide site-specific training using an evidence based course, or intervention. Multidisciplinary team meetings can be a great opportunity to identify eligible patients for cancer trials.*

## **5. Outcome measures**

Choosing the correct primary and secondary outcome measures for trials in surgical oncology ensure meaningful, patient-centred trial design (42). The Core Outcome Measures in Effectiveness Trials (COMET) initiative has facilitated the development and application of a number of 'core outcome sets' (COS) for malignant diseases through Delphi consensus processes (43-46). A COS is an agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population (47). Quality of life (QOL) measures are now routinely included within core outcome sets. A well designed QOL measure should be reliable

(measures what is intended to measure), valid (measures the correct outcome), and responsive (changes in response to changes in a patient's condition)(48). These can be generic health-related QOL measures such as EQ-5D or SF-36, disease-, or system-specific. Disease- or system-specific measures tend to have a better sensitivity and specificity than generic measures, but do often do not give an overall sense of patient wellbeing (49). All tested outcomes should be prospectively included within the trial protocol, and reported in accordance with this protocol, without deviation (50).

In organ preservation trials in rectal cancer surgery versus radical surgery to date QoL measures are largely missing, or use tools without validation, or with a poor magnitude of difference. The STAR-TREC study will collect a panel of disease and system specific QoL measures, including EORTC QLQ CR29 & C30, LARS score and ICIQ-MLUTS. Use of generic QoL measures such as EuroQol EQ-5D will aid assessment of the broader impact of treatment.

***Recommendation:*** *Where possible, include disease-specific, validated quality-of-life measures, complemented by a generic QOL measure as co-primary or secondary endpoints in trial design, guided by your public and patient representatives.*

## **6. Patient and public representation**

Patient and public involvement (PPI) in research ensures that we are 'experimenting with' not 'experimenting on' patients (51). Mismatch between clinicians and patients in identifying research topics(52) is particularly relevant in colorectal surgery, where potential benefits of treatment are counterbalanced by potentially deleterious effects on long-term quality of life. In 2015, the UK National Institute of Health Research launched a strategic review of Patient and Public Involvement in research, producing

the document 'Going the Extra Mile' (53). This focussed on embedding PPI in the culture of research design and conduct, and improving access and strategy for effective involvement. PPI has been demonstrated to have a multitude of benefits to trials, improving study design, communication with participants, recruitment, interpretation and communication of results (54). Patient involvement in responsive (e.g. advisory groups) and managerial (e.g. trial management groups) have been demonstrated to be more impactful in clinical trials than in oversight roles (e.g. trial steering committee)(55).

For STAR-TREC, the importance and relevance of the organ sparing surgery for early rectal cancer was endorsed at a national patient, public and charity involvement meeting (56). The trial development and management groups both incorporated PPI representatives to ensure the design and delivery of patient orientated research. Patient involvement was specifically impactful in choosing primary endpoints, determining an acceptable frequency of surveillance, and in quality-assuring patient facing information; this often lacks the clarity required for informed decision making (57). When planning a trial in surgical oncology, consider not only the involvement of PPI representatives in research design and conduct, but also the training and continuing development needs they will have to complete the role.

***Recommendation:*** *Embed patient and public representation into every stage of your research programme to ensure impactful, patient-centred research.*



## **Trial Example 2: ROCSS**

*Reinforcement of Closure of Stoma Site. A randomised controlled trial of reinforcement of closure of stoma site using a biological mesh (ISRCTN46330337).*

### **Trial Summary**

ROCSS is a phase III randomised controlled trial to assess the effectiveness of placing a biological mesh at the site of stoma closure to prevent incisional herniation. Participants are randomised in a 1:1 ratio to:

1. Stoma site closure with a pre-peritoneal collagen mesh (Strattice®)
2. Standard stoma site closure with surgeon's choice of suture material.

The primary outcome measure is the rate of clinical herniation at 2 years postoperatively. A summary of challenges and recommendations can be found in table 1.

### **7. Trainee-led networks**

The ROCCS study was designed and delivered by the West Midlands Research Collaborative. Surgical research collaboratives are groups of doctors in surgical training that work together to deliver patient-level, multi-centre, protocol-driven research and audit projects. This approach allows for large numbers of patients to be included in short time periods, and permits greater generalisability than single-centre studies. Surgical research collaboratives exist across the UK (58), Europe (59-62) and are emerging in low-middle income environments (63-68). These trainee groups have played a key role in the delivery of several high-quality randomised trials to date (69-71).

The ROCSS study demonstrated the benefits of trainee-led research groups in the delivery of multicentre trials. Firstly, with the appropriate mentorship a research-active cohort of future trial leaders and recruiters emerged, each equipped with Good Clinical Practice training. Secondly, trainees are well represented at various points along the patient pathway (outpatient clinics, assessment units, emergency departments, inpatient wards, and operating theatres) and are therefore uniquely positioned to recruit and randomise eligible patients that may have been difficult to identify within traditional research models. Thirdly, the rotational nature of the UK surgical training system (spending six to twelve months in a single hospital before transferring to another) facilitated the dissemination of the trial around regional and national centres, and crosses political boundaries.

***Recommendation:*** *Collaboration with trainee-led networks supports the delivery of multicentre trials in surgical oncology and develops future research leaders.*

## **8. Randomisation**

The purpose of randomisation is to create broadly matched groups who have similar known and unknown factors that could influence study outcome. However, selection bias can still occur with dropout or crossover due to failure of allocation concealment, or pseudo-randomisation: use of predictable quasi-randomisation, such as allocation by date of birth, sealed envelopes, or medical record number. As such randomisation should occur close to the time of intervention to mask the patient's allocation (72).

In the ROCCS trial randomisation was performed by an investigator in the anaesthetic room at the point of induction. An independently administered online and 24-hour telephone randomisation service ensured randomisation concealment, and minimised risk of selection bias. A minimisation procedure was used to ensure

balance for clinically plausible factors effecting the primary endpoint; operative contamination, creation of a new stoma, or an emergency operation.

***Recommendation:*** Multimodal access to randomisations services (e.g. telephone and online), with minimum time from randomisation to the intervention optimises allocation concealment and minimises risk of selection bias.

## **9. Novel techniques and training**

Scientific evaluation of novel surgical interventions is complicated. Innovations can undergo iterative modifications, hold ambiguity in definition, lack consensus for outcome evaluation, vary significantly in response to operator capabilities, and be subject to strong treatment preferences. As a consequence, only 10.3% of implantable intraabdominal devices (such as biological mesh) are supported by evidence from a published RCT with low risk of bias (73).

The IDEAL (Idea-Development-Exploration-Assessment-Long term) collaboration (10, 13, 74) have described a five-stage, stepwise framework for the development and evaluation of surgical innovation. The 'Idea' stage: 1 deals with proof of concept and first-in-man studies. The 'Development' stage: 2a refines technical details as experience progresses, and the 'Exploration' stage: 2b defines a standardised, stable procedure, with the obstacles to a definitive trial addressed. The 'Assessment' stage: 3 explores effectiveness of the standardised innovation versus standard care in randomised clinical trial. 'Long-term' evaluation: 4 maintains surveillance of the innovation using prospective databases and registries to identify rare and late outcomes, and broadened the applicability of the technique to novel patient groups.

The ROCSS study, described a novel technique for the placement of intraperitoneal biological mesh to prophylactically reinforce stoma closure sites (75). The feasibility and internal pilot studies followed IDEAL recommendations for the development of innovation (phase 1 to 2b) before the full IDEAL phase 3 trial testing the 'stable' technique. A technical paper was produced from IDEAL 1 (Idea) and 2a (Development) phases (75). This described in detail the procedure and periprocedural care, from proof of concept to the first seven cases in humans, providing follow-up data on safety, technical and procedural success. Appropriate ethical approvals were sought. The IDEAL phase 2b study was described as part of an internal pilot trial (76) of 90 patients in eight hospitals. This feasibility study reported the ability to recruit to a phase 3 study (90 patients within 12 months), the ability to randomise (greater than 50% eligible patients randomised), and deliverability and safety of the novel mesh placement technique. This demonstrated community learning and maturation of the procedural steps. Early publication of blinded, short-term safety data minimised the risk of harm to future patients undergoing the novel procedure ahead full comparative effectiveness data being made available.

Dissemination of the ROCSS technique was a key consideration in delivery of a IDEAL phase 3 trial. The standardised technique was presented in full in a training video (77) and an instructional, illustrated technical guide was produced (75). Live training cases were recorded and made available to operators to facilitate rapid uptake. The trial management group performed one-to-one mentoring of local Principle Investigators (PI) during joint cases at site set-up visits, allowing real-time training with an expert operator. PIs then disseminated the technique further within their centres. After site visits, open workshops were made available for participating

surgeons to review the technique and local PIs were offered the opportunity to attend theatre within the trial Chief Investigators centre at their convenience. Self-reported adherence to the standardised technique allowed procedure-to-procedure monitoring and response to any procedural adaptations.

***Recommendation:*** Follow IDEAL recommendations for evaluation of surgical innovations. Carefully consider your investigator training strategy to ensure consistent application of the standardised technique.

## **10. Learning curves**

Variation in outcome following surgery can occur as a direct result of the skill-set of the operator. For novel techniques, a procedure-specific ‘learning curve’ effect can be seen up to the point of ‘expertise’. Interventions in IDEAL phase 3 trials should be ‘stable’ with operators performing this optimally before comparisons are made (i.e. proficient in both the control (stoma closure) and intervention (mesh closure) procedure). However, changes in performance over time can happen even for fully trained surgeons (78, 79). This means that technical performance can improve even in the ‘standard care’ arm of a trial involving a novel therapy, risking contamination of the control arm and masking of a positive effect (80).

Learning curves have been addressed by stipulating a minimum number of procedures performed for eligibility (78, 81), or by statistical adjustment for the learning curve effect by controlling for expertise and experience in the analysis of outcome measures (e.g. using Bayesian hierarchical models (78, 82)). Another solution has been proposed as ‘expertise-based designs’, where different expert operators in each centre perform each procedure, requiring stratification of randomisation by surgeon and by centre (83). The most common proxy for judging

the 'expertise' of surgeons in oncology trials is time (84), represented as the total number of cases performed inside and outside of the study period (accessible via surgeons' logbooks). Other proxies have included the number of cases performed annually in the centre (accessible via national hospital-level statistics and national registries), the level of training of the operating surgeon (according to local, or national hierarchies of training), specific intra- or post-operative outcomes or via workplace based competency assessments (84, 85). Qualitative research may also assist the definition of procedure-specific technical proficiency (86).

In the ROCSS trial, the protocol mandated that the operating surgeon should have performed a minimum of 20 previous stoma closures, in line with consensus process amongst the Trial Steering Group. *A priori* learning effect analyses will determine any case-volume relationships in subsequent analyses.

***Recommendation:*** Case report forms should clearly record prior experience of participating surgeons. Pre-defined learning curve analyses improve generalisability of study findings and lead to more accurate treatment effect estimates by adjusting for a large source of variability.

## **11. Blinding**

Blinding (concealment of a patients group allocation after randomisation) can be difficult in surgical trials and introduce performance or detection bias (87). Typically blinding is considered in three dimensions; blinding of the patient, blinding of the operator, blinding of the outcome assessor (88). In surgical trials, blinding of the surgeon and the patient can be difficult. For example, tested groups may have different scars, or go through different treatment pathways. This can lead to differences in patient behaviour, responses to treatment and reporting of adverse

events. More subjective measures such as quality of life measures are most subject to measurement bias when compared to definite endpoints (e.g. mortality). In the ROCSS trial as the stoma site closure was performed through the same incision, it was possible to blind the patient, but not the surgeon to the group allocation. Creative techniques for trials where incisions or repairs are visibly different between group such as standardisation of wound dressings have been employed with some success (89). Placebo controlled surgical trials with 'sham surgery' have also been performed (90), however there is a number of ethical concerns in the setting of surgical oncology. Outcome assessment is the easiest stage to blind within surgical trials. In the ROCSS trial blinded review of cross-sectional imaging for evidence of hernia recurrence was performed by consultant radiologists.

***Recommendation:*** *Blinding of outcome assessors is an easy way of maximising internal validity in surgical trials. Innovative methods for achieving blinding in surgical trials have been demonstrated.*

## **12. Follow-up**

Loss to follow-up presents a major risk to internal validity as it leaves a specific population where the primary outcomes remains unassessed (for example those that have died, suffered significant morbidity, or moved abroad). Attrition bias occurs where different groups are lost to follow-up in different treatment arms. The ROCCS trial was susceptible to patient loss at follow-up, as assessment of the primary outcome, clinical stoma site herniation, was recorded 2 years postoperatively.

In order to improve concordance with follow-up in ROCSS, patients who missed their initial follow-up appointment at 2 years were offered a small financial incentive (£20GBP gift voucher) in exchange for attendance. This dramatically improved

adherence to follow up, and reduced research waste (i.e. missed appointments, clinical and administrative burden). It has been previously demonstrated that selective monetary incentivisation can improve adherence to follow-up in interventional studies in a cost-effective manner (91). Other strategies described include recorded delivery of postal questionnaires, personalised approaches, non-monetary incentives, prize-draws, behavioural motivators, additional reminders, however evidence for the benefit of these is unclear upon meta-analysis (92). Within our experience, patient centred approaches to follow-up such as combining outcome assessment with routine appointments may also improve concordance. Any patients lost to follow-up despite these efforts were included within the trial CONSORT diagram, with specific explanations given for each (93).

***Recommendation:*** Consider including strategies for maximising concordance with primary outcome assessment (e.g. selective monetary incentivisation) within your funding application.



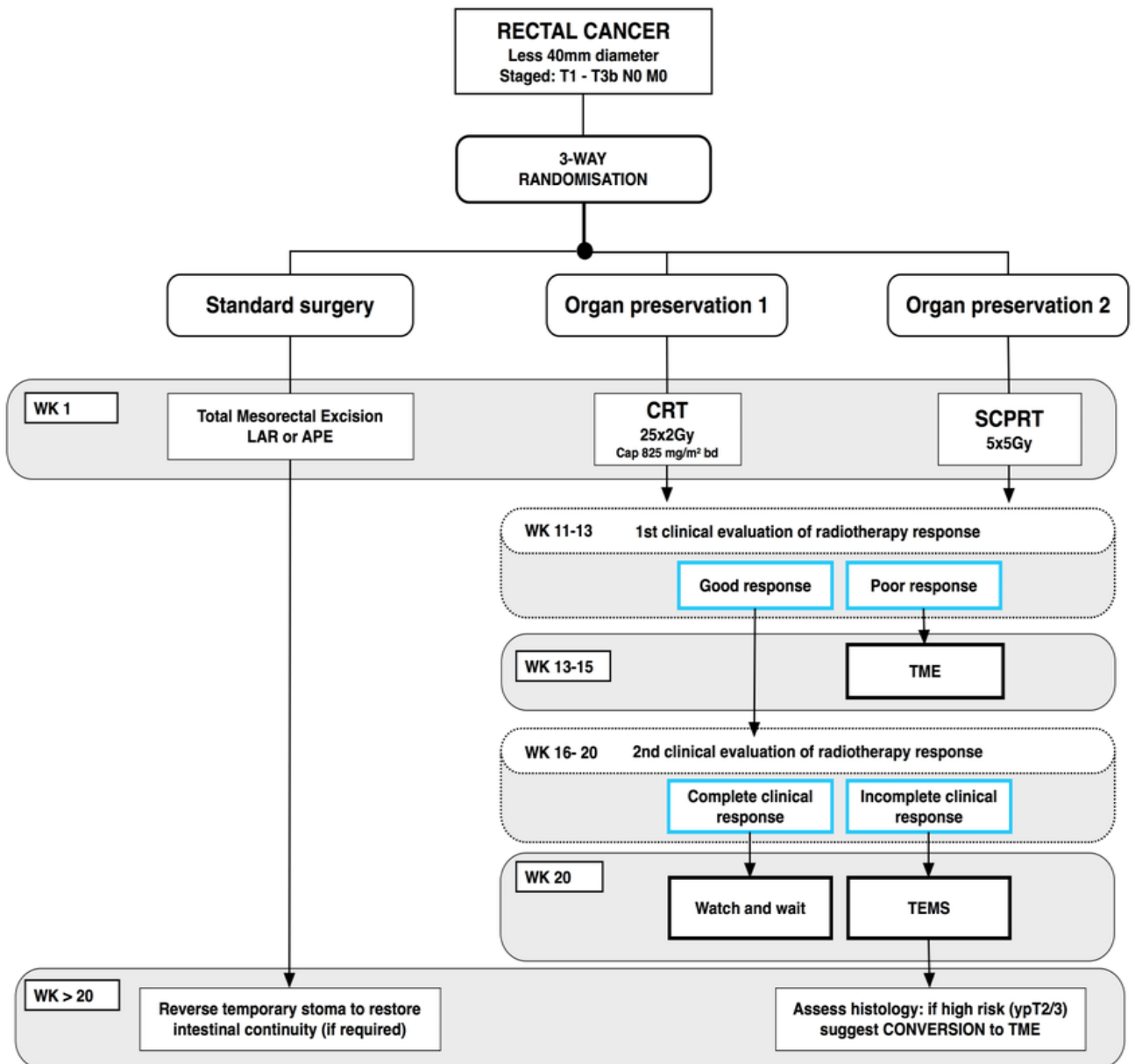
## **Conclusion**

Whilst pragmatic randomised controlled trials offer the ability to compare high quality clinical effectiveness data between well-matched groups, trials in surgical oncology face significant methodological challenges and should be designed and interpreted with caution in light of these. The quality and volume of surgical trials have been improved significantly by targeted methodological research over the past two decades. Better understanding of the challenges facing trials comparing operative versus non-operative management, and novel surgical techniques in the treatment of cancer will accelerate high quality evaluation, and maximise benefit for the greatest number of patients.

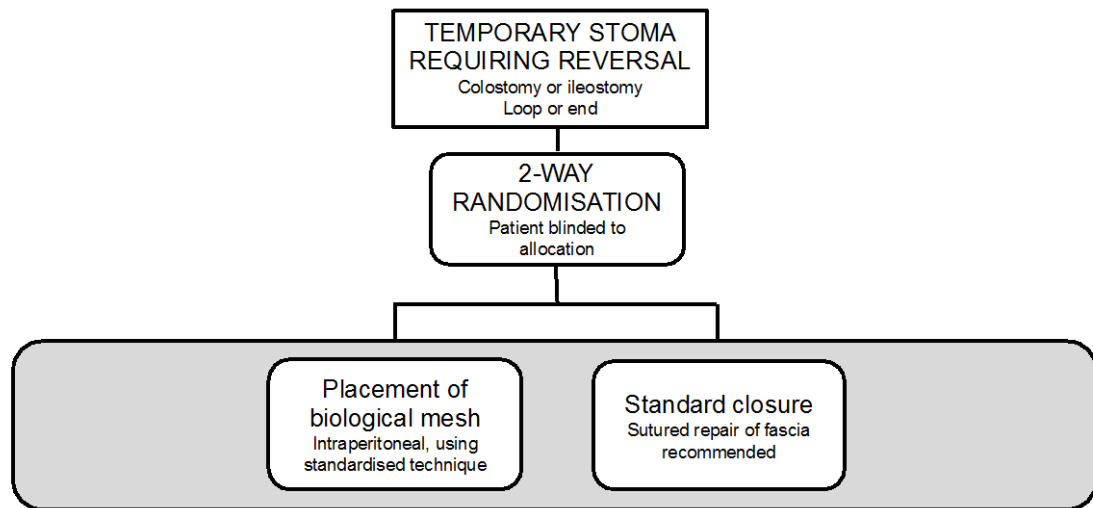
**Table 1. Recommendations for randomised trials in surgical oncology**

	<b>Challenge</b>	<b>Recommendation</b>
<b>1</b>	Standardisation of technique	<i>A pragmatic design in surgical trials facilitates the direct implementation of effectiveness data into practice. Standardisation of a procedural technique with a structured typology ensures high-quality reporting and patient-level meta-analysis.</i>
<b>2</b>	Pilot and feasibility studies	<i>Consider a feasibility study, with an internal or external pilot phase, where there is uncertainty about the deliverability of a main trial.</i>
<b>3</b>	Balancing treatments	<i>Prepare balanced explanations for both operative and non-operative treatments. Restoring patient equipoise is possible if they have incomplete information about one of both of the study arms.</i>
<b>4</b>	The recruitment pathway	<i>Embed recruitment training into your site set-up package. Once set-up, identify sites where recruitment rates are low, and provide site-specific training using an evidence based course, or intervention. Multidisciplinary team meetings can be a great opportunity to identify eligible patients for cancer trials.</i>
<b>5</b>	Outcome measures	<i>Where possible, include disease-specific, validated quality-of-life measures, complemented by a generic QOL measure as co-primary or secondary endpoints in trial design, guided by your public and patient representatives.</i>
<b>6</b>	Patient and public representation	<i>Embed patient and public representation into every stage of your research programme to ensure impactful, patient-centred research.</i>
<b>7</b>	Trainee-led networks	<i>Collaboration with trainee-led networks supports the delivery of multicentre trials in surgical oncology and develops future research leaders.</i>
<b>8</b>	Randomisation	<i>Multimodal access to randomisations services (e.g. telephone and online), with minimum time from randomisation to the intervention optimises allocation concealment and minimises risk of selection bias.</i>
<b>9</b>	Novel techniques and training	<i>Follow IDEAL recommendations for evaluation of surgical innovations. Carefully consider your investigator training strategy to ensure consistent application of the standardised technique.</i>
<b>10</b>	Learning curves	<i>Case report forms should clearly record prior experience of participating surgeons. Pre-defined learning curve analyses improve generalisability of study findings.</i>
<b>11</b>	Blinding	<i>Blinding of outcome assessors is an easy way of maximising internal validity in surgical trials. Innovative methods for achieving blinding in surgical trials have been demonstrated.</i>
<b>12</b>	Follow-up	<i>Consider including strategies for maximising concordance with primary outcome assessment (e.g. selective monetary incentivisation) within your funding application.</i>

**Figure 1. STAR-TREC Trial Schemata**



**Figure 2. ROCSS Trial Schemata**



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